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DETAILED REVIEW DOCUMENT ON CLASSIFICATION IN OECD MEMBER COUNTRIES OF
SUBSTANCES AND MIXTURES WHICH CAUSE RESPIRATORY TRACT IRRITATION AND
CORROSION

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**DETAILED REVIEW DOCUMENT ON CLASSIFICATION IN OECD MEMBER
COUNTRIES OF SUBSTANCES AND MIXTURES WHICH CAUSE RESPIRATORY
TRACT IRRITATION AND CORROSION**

Environment Directorate

Organisation for Economic Co-operation and Development

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The work of the OECD related to chemical safety is carried out in the Environment, Health and Safety Programme. As part of its work on chemical testing, the OECD has issued several Council Decisions and Recommendations (the former legally binding on member countries), as well as numerous Guidance Documents and technical reports. The best known of these publications, the OECD Test Guidelines, is a collection of methods used to assess the hazards of chemicals and of chemical preparations. These methods cover tests for physical and chemical properties, effects on human health and wildlife, and accumulation and degradation in the environment. The OECD Test Guidelines are recognised world-wide as the standard reference tool for chemical testing.

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DETAILED REVIEW DOCUMENT ON CLASSIFICATION IN OECD MEMBER COUNTRIES OF SUBSTANCES AND MIXTURES WHICH CAUSE RESPIRATORY TRACT IRRITATION AND CORROSION

SCOPE AND DEFINITIONS

Scope

1. This endpoint covers substances [and preparations] that cause irritation of the upper respiratory tract in humans.

DESCRIPTION OF THE CLASSIFICATION SYSTEMS IN PLACE

The EU system (including Slovenia):

2. The development of the R phrase, R37, Irritating to respiratory system within the EU is detailed in Appendix 1. The current criteria are as follows:

R 37: Irritating to respiratory system:

Is assigned to substances and preparations which cause serious irritation to the respiratory system based on:

- a) practical observation in humans
- b) positive results from appropriate animal tests

Comments regarding the use of R37:

In interpreting practical observations in humans, care should be taken to distinguish between effects which lead to classification with R48⁽¹⁾ from those leading to classification with R37. Conditions normally leading to classification with R37 are reversible and usually limited to the upper airways.

Positive results from appropriate animal tests⁽²⁾ may include data obtained in a general toxicity test, including histopathological data from the respiratory system. Data from the measurement of experimental bradypnea⁽³⁾ may also be used to assess airway irritation.

⁽¹⁾ R48 = *Danger of serious damage after repeated or prolonged exposure.*

⁽²⁾ *Appropriate animal tests could include an acute inhalation toxicity study, a repeated-exposure inhalation study.*

⁽³⁾ *The 'Alarie assay'.*

3. As a general observation, historically, for Existing Substances the data that were used as a basis for classification with R37 were mainly based on human experience. However, in recent years there has been an increasing reliance on the use of information from animal studies. For New Substances, it is highly unlikely that there will be human experience information, hence classification is based on other sources of information such as experimental studies in animals, or prediction based on corrosivity (to skin/eyes).

4. For mixtures, the health effect data required for classification and labelling may be obtained by the application of test methods indicated above. Classification may also be obtained by application of methods indicated in Part B of Directive 1999/45/EC ('The Preparations Directive'), '*Concentration limits to be used in evaluation of health hazards*'. This sets out specific concentration limits for gaseous and non-gaseous mixtures (or preparations). In short, a mixture may be classified as 'R37, Irritating to the Respiratory Tract' if that mixture contains more than a specified percentage concentration of a substance that has been classified as 'Corrosive' (see Appendix 2).

The US System

5. In the USA, there is no classification specifically for this endpoint; it is handled as a target organ effect, based mainly upon human experience. In the USA, for the Occupational Safety and Health Administration (OSHA) and Consumer Product Safety Commission (CPSC), target organ effects lead to identification of the specific organ on the label. The various precautionary statements and statements of treatment can be organized in a specific manner. Hence, respiratory tract irritation is covered in this manner.

The Canadian System

6. The Canadian Workplace Hazardous Materials Information System (WHMIS) includes provisions for "chronic toxic effects". A chronic toxic effect is defined as an adverse effect on the health of a person or test animal that develops over time, following a single exposure to a toxic substance, or after prolonged or repeated exposure to a toxic substance under conditions that do not produce the same effect from a single exposure. Adverse health effects in this category include life-threatening or serious impairment of body organs and the cardiovascular or nervous system. Respiratory tract irritation would fall into this hazard class.

The criteria for substances or tested mixtures for this hazard class are detailed in Appendix 3.

UN Transport of Dangerous Goods

7. In the UN transport regulations irritation of the respiratory system (RTI) is covered indirectly via the subsidiary corrosive risk for toxic gases. Toxic gases are:

Gases

- which are known to be so toxic or corrosive to humans as to pose a hazard to health; or
- which are presumed to be toxic or corrosive to humans because they have an LC₅₀ value equal to or less than 5,000 ml/m³ (ppm).

Gases meeting the above criteria owing to their corrosivity are to be classified as toxic with a subsidiary corrosive risk.

Mixtures of gases:

A gas mixture has a subsidiary risk of corrosivity when the mixture is known by human experience to be destructive to the skin, eyes or mucous membranes or when the LC₅₀ value of the corrosive components of the mixture is equal to or less than 5,000 ml/m³ (ppm) when the LC₅₀ is calculated by a formula using mol fractions and LC₅₀ values.

APPENDIX 1: DEVELOPMENT OF R37, IRRITATING TO THE RESPIRATORY SYSTEM

Within the EU, the first general definition of "irritating" in Directive 67/548/EEC (27 June 1967) was recorded as "Non-corrosive substances and preparations which, through immediate, prolonged or repeated contact with the skin or mucous membrane, may cause inflammation". The respective R(-isk) phrase was initially R84 = Irritating to skin, eyes and respiratory system.

Directive 76/907 (14 July 1976): Creation of new (separate) R phrase: R37 = Irritating to respiratory system.

Directive 83/467 (16 Sept. 1983): For the first time a criterion was introduced: "Substances and preparations which cause serious irritation to the respiratory system, based normally on practical observation." This means that at that time data from animal experiments were not regarded to be useful in classification for this endpoint.

Directive 93/21/EEC (27 April 1993): R37 is slightly modified. New criteria: "Substances and preparations which cause serious irritation to the respiratory system, based normally on practical observation in humans".

Directive 96/54/EEC (30 July 1996):

Positive results from appropriate animal tests were for the first time introduced. Thus, test results in inhalation toxicity studies including histopathological investigations can be used for classifying purposes.

New expanded criteria were established in order to discriminate classification between respiratory irritation and R48 = Danger of serious damage to health by prolonged exposure.

Furthermore, the Alarie test was introduced as a basis for respiratory irritation.

The revised criteria, which are valid up to now are (as laid out in EU guidance documents):

'R 37: Irritating to respiratory system

Is assigned to substances and preparations which cause serious irritation to the respiratory system based on:

- practical observation in humans
- positive results from appropriate animal tests

Comments regarding the use of R37:

In interpreting practical observations in humans, care should be taken to distinguish between effects which lead to classification with R48 (see section 3.2.4.) from those leading to classification with R37. Conditions normally leading to classification with R37 are reversible and usually limited to the upper airways.

Positive results from appropriate animal tests may include data obtained in a general toxicity test, including histopathological data from the respiratory system. Data from the measurement of experimental bradypnea may also be used to assess airway irritation.'

APPENDIX 2: CLASSIFICATION OF MIXTURES (PREPARATIONS) WITHIN THE EU

(Taken from Directive 1999/45/EC of the European Parliament and of the Council, published in the Official Journal of the European Communities, 30/7/1999)

Non-gaseous mixtures:

Classification of the substance	Classification of the mixture (preparation)			
	C with R35	C with R34	Xi with R41	Xi with R36, R37, R38
C with R35	Concentration $\geq 10\%$ R35 obligatory	$5\% \leq$ concentration $< 10\%$ R34 obligatory	5% (*)	$1\% \leq$ concentration $< 5\%$ R36/38 obligatory
C with R34		Concentration $\geq 10\%$ R34 obligatory	10% (*)	$5\% \leq$ concentration $< 10\%$ R36/38 obligatory

Classification of the substance	Classification of the mixture (preparation)			
	C with R35	C with R34	Xi with R41	Xi with R36, R37, R38
C with R41			Concentration $\geq 10\%$ R41 obligatory	$5\% \leq$ concentration $< 10\%$ R36 obligatory
C with R36, R37, R38				concentration $\geq 20\%$ R36, R37, R38 are obligatory in the light of the concentration present if they apply to the substances under consideration

(*) According to the labelling guide (Annex VI to Directive 67/548/EEC), corrosive substances assigned risk phrases R35 or R34 must also be considered as being assigned phrase R41. Consequently, if the preparation contains corrosive substances with R35 or R34 below the concentration limits for a classification of the preparation as corrosive, such substances can contribute to a classification of the preparation as irritant with R41 or irritant with R36.

Gaseous mixtures:

Classification of the substance (gas)	Classification of the gaseous mixture (preparation)			
	C with R35	C with R34	Xi with R41	Xi with R36, R37, R38
C with R35	Concentration $\geq 1\%$ R35 obligatory	$0.2\% \leq$ concentration $< 1\%$ R34 obligatory	$0.2\% (*)$	$0.02\% \leq$ concentration $< 0.2\%$ R36/37/38 obligatory
C with R35		concentration $\geq 5\%$ R34 obligatory	$5\% (*)$	$0.5\% \leq$ concentration $< 5\%$ R36/37/38 obligatory
C with R41			Concentration $\geq 5\%$ R41 obligatory	$0.5\% \leq$ concentration $< 5\%$ R36 obligatory
Xi with R36, R37, R38				concentration $\geq 5\%$ R36, R37, R38 obligatory as appropriate

(*) According to the labelling guide (Annex VI to Directive 67/548/EEC), corrosive substances assigned risk phrases R35 or R34 must also be considered as being assigned phrase R41. Consequently, if the preparation contains corrosive substances with R35 or R34 below the concentration limits for a classification of the preparation as corrosive, such substances can contribute to a classification of the preparation as irritant with R41 or irritant with R36.

Appendix 3**Canadian Workplace Hazardous Materials Information System**

Basis for Evaluation	"Very Toxic Material"	"Toxic Material"
ORAL ROUTE OF EXPOSURE 1. Subchronic Oral Toxicity – <i>Rodent OECD Test Guideline 408</i> 2. Subchronic Oral Toxicity – <i>Non-Rodent OECD Test Guideline 409</i> 3. Oral Route Test – <i>OECD Test Guideline 452</i>	Dose of not more than 10 mg per kg of weight of test animal per day	Dose of more than 10 but not more than 100 mg per kg of weight of test animal per day
DERMAL ROUTE OF EXPOSURE 1. Subchronic Dermal Toxicity – <i>OECD Test Guideline 411</i> 2. Dermal Route Test – <i>OECD Test Guideline 452</i>	Dose of not more than 20 mg per kg of weight of test animal per day	Dose of more than 20 but not more than 200 mg per kg of weight of test animal per day
INHALATION ROUTE OF EXPOSURE 1. Subchronic Inhalation Toxicity – <i>OECD Test Guideline 408</i> 2. Inhalation Route Test – <i>OECD Test Guideline 452</i>	Concentration of not more than 25 ppm by volume of a gas or vapour, or not more than 10 mg/m ³ of a dust, mist or fume.	Concentration of more than 25 ppm but not more than 250 ppm by volume of a gas or vapour, or more than 10 mg/m ³ but not more than 100 mg/m ³ of a dust, mist or fume.